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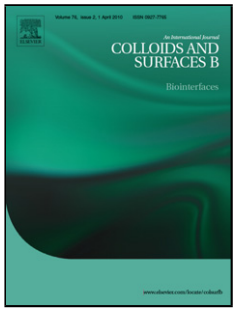

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Nano-suspension coating as a technique to modulate the drug release from controlled porosity osmotic pumps for a soluble agent

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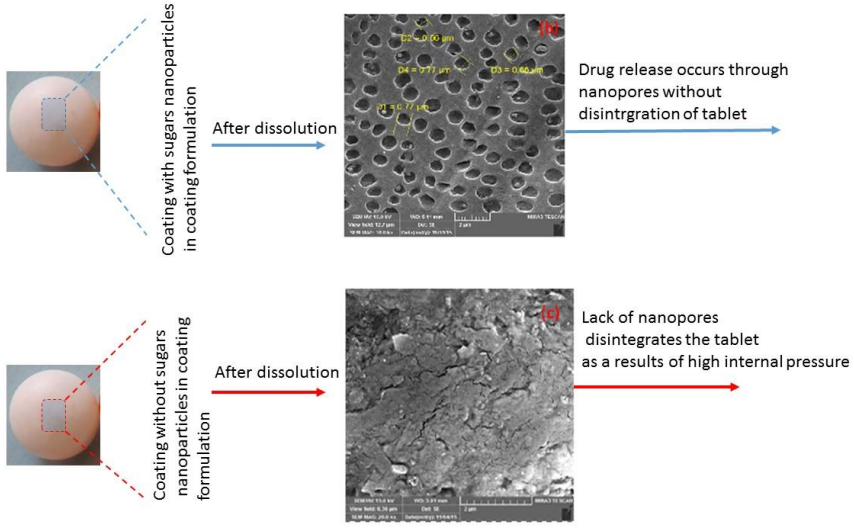
Highlights

- Hydrophilic pore formers in nano range was prepared using ball mill
- Pore former concentration in the coating had crucial effect on coating integrity
- Gelling agent concentration in the coating had crucial effect on coating integrity
- Nanosuspension coating tackle the issue associated with conventional osmotic pump

Grasphical abstract



Abstract

In controlled porosity osmotic pumps (CPOP), usually finding a single solvent with a capability to dissolve both film former (hydrophobic) and pore former (hydrophilic) is extremely challenging. **Therefore, the aim of the present investigation was to tackle the issue associated with controlled porosity osmotic pump (CPOP) system using nano-suspension coating method. In the present study 4-Amino pyridine was used as a highly water soluble drug.** In this method, a hydrophilic pore former (sucrose or mannitol) in nano range was suspended in polymeric coating solution using ball-mill. The performance of the prepared formulations was assessed in terms of D_{12h} (cumulative release percent after 12 **hours**), Dev_{zero} (mean percent deviation of drug release from zero order kinetic), t_L (lag time of the drug release) and RSQ_{zero}. The results revealed that gelling agent amount (HPMC E_{15LV}) in core and pore former concentration in SPM had crucial effect on SPM integrity. **All the optimised formulations showed a burst drug release due to fast dissolving nature of the pore formers.** Results obtained from

scanning electron microscopy demonstrated the formation of nanopores in the membrane where the drug release takes place via these nanopores. Nano suspension coating method can be introduced as novel method in formulation of CPOPs.

Keywords: Drug Delivery; Controlled Porosity Osmotic Pumps (CPOPs); Nano-suspension coating, Drug Release

1. Introduction

In recent years, novel drug delivery systems (NDDS) have gained great attention due to providing sustained and constant drug release. Among NDDS, per oral controlled release (CR) systems including matrices, reservoirs and osmotic devices allocated the foremost market segment because of their advantages over others delivery systems [1]. On the other hand, the drug release from other delivery systems can be affected by the presence of food, pH and other physiological factors. The independency of these factors to a large extent in the case of osmotic systems is considered as advantages [2, 3].

Osmotic pumps devices can be very useful for delivery of drugs, particularly for drugs with short biological half-life which requires frequent consumption during 24 hours [4]. Many different systems have been developed based on the principle of osmotic pressure and some of these systems have reached the market. Elementary osmotic pump (EOP) [5-7], sandwiched osmotic tablet system (SOTS) [8], push-pull systems (PPOP) [9-12], controlled porosity osmotic pumps (CPOP) [13, 14], tablet in tablet (TNT) cores [15], Asymmetric membrane capsule for osmotic drug delivery [12, 16], osmotic systems made by swellable-core technology [17] and swellable elementary osmotic pump(SEOP) [18, 19] can be noted. An EOP device principally consists of an osmotically active core covered by a semipermeable membrane (SPM) generally composed of cellulose acetate as film former and a small orifice drilled by laser beam or

mechanical drills [2, 20]. Controlled porosity osmotic pumps (CPOPs) are very simple forms of osmotic systems which the delivery orifice is formed by the incorporation of a water-soluble component in the membrane [21, 22]. Thus, there is no need for sophisticated equipment for drilling of SPM. Other advantages of this system over EOPs are the drug release occurs from the entire surface of the membrane consequently decreasing the chance of pore-blocking which generally leads to release stop or system cracking. Once the tablet exposes to the aqueous media, the hydrophilic component dissolves and produces microscopic holes in SPM for release of drug solution [23, 24]. The main polymer in (CPOP) construction is a hydrophobic polymer to form a semi-permeable membrane which is completely insoluble in water such as cellulose acetate or cellulose acetate butyrate [25]. Liquid coating (solvent system) should be an organic solvent such as acetone with low polarity or a combination of non-polar solvents in order to solve this polymer [23]. Due to the very low water solubility of these polymers even a small amount of water in the composition of the coating liquid cannot be used. The other main ingredients used in the formulation of semi-permeable membrane for this kind of osmotic systems are pore formers that after exposing the tablet to aqueous solutions (dissolution medium) can produce pores to release the drug [24]. Therefore, these materials should have high water solubility leading to the drug release in aqueous media instantly.

Technical problem in the preparation of these tablets is simultaneously dissolving lipophilic film former and hydrophilic pore formers in one solvent system. Using highly water soluble materials as pore formers in the SPM composition can result in reduction of the lag time of drug release from CPOP systems and increasing amount of released drug from CPOPs. Since the used pore formers with high solubility in water have a low solubility in acetone-ethanol solvent thus in the present study an attempt was made to employ nano-sized pore former solid particles suspended in a polymer solution to tackle the release issue. The micro-sized pore former particles suspended in polymeric solution has already been applied in our research lab [26], but in the present study, the authors have focused on employing nano-sized pore former to control the porosity of the membrane in osmotic systems.

2. Materials and Methods

2.1 Materials

4-Amino pyridine **(purity >99%)** was obtained from Merck Chemicals (Germany). Cellulose acetate with 40 % acetyl groups (Fluka, Switzerland) was used as film former polymer (SPM). Hydroxypropyl methylcellulose (HPMC E_{15LV}) (Colorcon, England) was used as water-swellable polymer and gelling agent. Polyethylene glycol (PEG) 200 **(Pharmaceutical grad)** and castor oil **(Pharmaceutical grade;** Merck, Germany) were used as plasticizer. Avicel PH101 (Blanver, Korea) was used as compressibility enhancer. Other material such as acetone **(HPLC grade)**, **absolute** ethanol **(HPLC grade), talc (purity 98%)** and lactose **monohydrate (Pharmaceutical grade)** were purchased from Merck Company (Germany). Sucrose and mannitol **(Pharmaceutical grade;** Merck, Germany) were used as a solid pore former in formulation of SPM with different percentages. Sucrose was applied as osmotically active agent in core tablet formulation.

2.2 Preparation of core tablets of osmotic systems

4-Amino pyridine powder was micronized by jet mill (Fritsch FE80N, Germany) before using in tableting process. Drug powders along with other core ingredients were mixed thoroughly for 10 min by mortar and pestle. Then the mixture was compressed into biconvex tablets using a single tablet press (Korsch, Germany) with 9 mm diameter oval biconvex punches. The final weight of each tablet was kept at 465 mg in order to have a similar volume and surface area for the tablets. All of the core formulations contained 20 mg 4-Amino pyridine. The hardness of all prepared tablets was adjusted in the range of 6-8 Strong Cobb.

2.3 Coating of core tablets

The prepared core tablets were coated with a coating suspension containing cellulose acetate, castor oil, PEG200 and nano-suspended sucrose or mannitol in acetone/ethanol mixture (90:10) employing dip coating technique. **In this technique,** the cores were fixed with micro-drill **(micro drill diameter was around 350 µm and held by a hand piece)** and floated into coating suspension for 5 seconds with a gentle horizontal rotation and drying at room temperature. This step was repeated **several** times until the intended membrane thickness (125 ± 10 µm) was achieved. **Micro-drills were pulled out from the coated tablets by rotating hand piece and the created micro pore was sealed by small amount of coating solution.** The same condition was maintained during coating of all tablets and thickness of membrane was periodically checked using digital micrometer (Mitotoyo, Japan) with high accuracy (0.001 mm). Cellulose acetate (6 g) and plasticizers namely, castor oil (3 %w/v), and PEG200 (2 %w/v) were dissolved in 100 ml of coating liquid. Due to poor solubility of sucrose in this solvent mixture and preparing nano-suspension, the sucrose particles was suspended in the acetone/ethanol mixture (90:10 v/v) inside the ball-mill chamber (Retsch® PM100, Germany). The volume of the chamber was 25 ml containing 8 balls with 10 mm diameter. The sample was ground for 3 hours at 350 rpm, and at 10 min intervals a diverse rotation was applied.

During dip coating process the coating suspension was continuously stirred to maintain a good uniformity while using in the process. The core and SPM compositions for different formulations are presented in Table 1.

2.4 Particle Size Analyzing

The particle size of sucrose and mannitol particles suspended in acetone/ethanol mixture after grinding in ball-mill was measured using Shimadzu-Japan (SALD-2120) and the results are demonstrated in Figure1.

2.5 Scanning electron microscopy (SEM)

SEM images were prepared from selected and blank formulations using Tescan (Czech Republic) apparatus with different magnifications after exposing the tablets to the aqueous media in order to assess the size and shape of pores formed by dissolving the pore formers in SPM structure. Prior to assessment **with acceleration voltage of 15.0 kV,** the samples were prepared on aluminum stubs and coated with gold **using sputter gold coating method**.

2.6 *In vitro* release test

In vitro release studies were carried out using a dissolution apparatus II paddle method (Erweka DT-6 R, Germany), set at 100 rpm (rotating speed) and 900 mL distilled water maintained at 37 ± 0.1°C. At different time intervals (5, 10, 15, 45 minutes and 1, 1/5, 2, 4, 6, 8, 10, 12, and 24 h) 5 ml of the dissolution medium were withdrawn and analyzed spectrophotometrically (UV spectrophotometer, Shimadzu Mini 1240, Japan) at 260.8 nm. The withdrawn dissolution medium was instantly replaced by the same volume of the fresh medium. The release test was performed at least for 3 tablets and the corresponding mean and standard deviations (SD) were calculated.

2.7 Mathematical treatments

The release profile of a perfect osmotic system should follow zero order kinetics for a period of at least 12 h with a majority of drug should be release within this period. Formulations with acceptable stability and release pattern were selected for further evaluations. As an ideal osmotic system should possess the ability to release a high percentage of drug content with a constant release rate (zero order kinetics) in the period of 12 h with low lag time, therefore, comparative parameters including D_{12h} (percent of the drug released within 12), t_L (lag time of the drug release from device), RSQ_{zero} (R square of release data fitted to zero order equation) and Dev_{zero} (mean percentage deviation of the release data from zero order release), were

calculated to evaluate the performance of the formulations. Lag time defines as time required to reach steady state drug release from osmotic devices. Dev_{zero} was calculated based on:

Dev_{zero} (%) =100/N$\sum$ 〖$(Q_{calc}-Q_{obs})/Q_{obs}$〗

Where Q_{obs} is the value of measured amount of drug released in each sampling time, Q_{calc} is the calculated amount of the drug released according to zero order equation for the same time and N is the number of sampling times.

3. Results and Discussion

3.1 Particle size analyzing

Figure 1 demonstrated the particle size distribution of prepared the nano-suspended sucrose and mannitol particles. The results showed that the mean volume diameters of nano-sized sucrose and mannitol were 476 and 511 nm respectively. This was in a good agreement with the size of pore generated after the dissolution of SPM as confirmed by SEM and discussed below.

3.2 Scanning electron microscopy (SEM)

SEM images from SPM were obtained after 12 h exposure to the dissolution medium. Based on Figure 2, the nano-pores were formed in the membrane due to the dissolution of mannitol and sucrose nanoparticles in the membrane structure and the diameter of pores (600-700 nm) are close to the size of sucrose and mannitol nanoparticles in the coating suspension shown in Figure 1. SEM images of F24 (blank SPM, Figure 2c) showed no pores which could be due to the absence of pore former in the formation. Figure 2c also shows that the system contains lots of crack at the surface of the device after the dissolution which could **be because of** a high internal osmotic pressure arising from the swelling of the polymer in the core of tablet leading to the formation of cracks in SPM. The presence of cracks led to the system expulsion in less than one hour leading to dose dumping which will be discussed in the relevant section below. These

images were comparable to those reported in previous articles for CPOP systems formulated with other commonly used pore formers [26, 27, 28].

2.4 Effect of core formulation and pore former concentration on drug release

Drug release profiles of 4-amino pyridine from osmotic formulations containing different concentrations of sucrose as a pore former (F1 to F4) in the coating liquid were shown in Figure 3a. According to this Figure, by increasing pore former concentration from 1% (F4) to 8% (F1), drug release rate increased during the first 120 min. Drug release rate from all mentioned formulations were faster than the desired rate probably due to a higher internal pressure. This high pressure may also be responsible to system cracking as described before. These formulations cracked in the first two hours due to the high amount (50 mg) of polymer which caused high swelling pressure after the exposure to the dissolution medium. These formulations also had higher osmotic pressure due to the higher content of the osmotic agent (sucrose) in their central cores.

An attempt was made to reduce the concentration of sucrose (an osmotic agent) from 175 mg to 100 mg in the core (F5-F9) to reduce the internal osmotic pressure and hence the drug release. At the same time, talc was also incorporated in the formulation**s** as a neutral filler to maintain the tablet weights in the range. The results showed that the percentage drug release reduced (compare Figures 3a and 3b) by decreasing the osmotic agent (sucrose) in the core formulation. This may be **described** as lower amount of sucrose in core tablet formulation created lower osmotic pressure gradient leading to the lower water imbibing rate into the system and consequently causing the decreased drug release.

As shown in figure 4, decreasing of osmotic agent from 175 mg to 100 mg caused a significant improvement in stability of the system against cracking (4 to 6 hours). Among F5 –F9, the formulations with lower amounts of pore former in their SPMs (F8 and F9 with 0.5 and 0.1% pore former) showed lower resistance against cracking.

Figure 4a demonstrates how by reducing the amount of HPMC in the core almost a similar release pattern can be obtained, although they have different concentrations of pore former (F10 and F11). Decreasing HPMC level from 50 mg to 20 mg in the core (F10-F11) caused an improvement in SPM resistance until 8 hours but all above formulations are not suitable for 12 h drug delivery because they lost their integrity during the dissolution run after a few hours. The appearance of the cracks in these systems are most likely due to the higher polymer swelling force leading to low resistance of SPM as these cracks can also be seen in formulations with less osmotic agent. But reducing the polymer amount in core tablets to 10 mg or elimination of the polymer resulted in very robust SPM. In addition, systems with lower or higher concentrations of sucrose (less than 2% or more than 6%) in their SPM formulation showed faster cracking in the tablets. It seems that higher percent of pore former in SPM, disintegrates the structure of SPM and lower percent of pore former disable to provide sufficient pores to relief the internal hydrostatic pressure leading to low SPM resistance and therefore cracking.

Figures 4b and 5 demonstrate the release profiles of F12-F16 (containing 10 mg HPMC in the core) and F18-F22 (without HPMC in the core). Formulations F12-F16 also contain different concentrations of pore former (0.1-4%). It seems that less resistance of SPM of F14 is related to the insufficient pores to evacuate the internal hydrostatic pressure. The better stability of F12 in comparison with F10 revealed that the amount of osmotic agent was the same (100 mg) and the only variable was the amount of polymer (20 and 10 mg for F10 and F12 respectively) which could be an important factor for resistance of the system during the dissolution process. With decreasing the polymer concentration in the core formulation, swelling force of polymer decreases and stability of the SPM against internal pressure of the system improves. This observation also indicates that the polymer swelling force probably was responsible for cracking of F10 and F11.

Among formulations F12–F16, F15 exhibited good characteristics such as acceptable D_{12h} (more than 75% drug release) and closest to zero order release pattern in comparison to the other formulations

(RSQ_{zero} = 0.99). The presence of HPMC in core formulations and formation of gel containing drug may result in low D_{12h} value in F13and F14 which contained higher amount of pore former (1.5 and 1% respectively).

Formulations F18-F22 (Figure 5) were prepared with no HPMC in their core tablets with pore-former concentration of 4-0.1% respectively. In this group of formulations, the internal hydrostatic pressure was in minimum level compared to others and thus, all of them maintained their integrity during 12h and F22 with 0.1% pore former demonstrated lowest release rate (5.77 mg/h) and D12 (69.26%). Optimum formulations were selected for evaluation of mannitol as pore-former (F17 and F23). Based on Figure 6, the data revealed that mannitol can also act as a pore-former. The comparative parameters of selected (resistant devices against cracking) formulations are illustrated in Table 2. The most important advantage of all optimized formulations using this novel nano-suspension coating is having negative lag time. This means that the drug release starts as soon as the device contacts with the dissolution medium which is a big advantage over other osmotic devices. The nano sized hydrophilic pore formers were able to dissolve immediately after the exposure to the aqueous media and produce pores for drug release during the first couple of minutes.

Although most of the coated tablets cracked, it is highly unlikely cracking can occur in the tablets over the period of time if the relative humidity is controlled. In case of storing these tablets on the shelf at very high relative humidity (e.g. 98%) if the tablet absorbs moisture from the environment there is a chance that tablets might crack.

Nowadays, porous materials are becoming more popular in tablet systems such as mesoporous silicon particles [29] as they can improve the dissolution of hydrophobic drugs and also enhance the permeability of large hydrophobic molecules [30]. Although, in the present study, the application of porous materials on the performance of osmotic pumps was not investigated, the authors suggest that it is important to compare the effect of inorganic porous materials in coating system with organic nanomaterials (used in the present study) on drug release

4. Conclusion

The applicable and effectiveness of the nano-suspension coating technique with glycosides in formulation of CPOP systems was verified by this study. The most essential parameters in these formulations were the amount of pore former in the membrane and gelling agent in the core formulation to achieve durable device. The most important achievement for the osmotic system using nano-suspension coating is the onset of drug release from CPOPs which occurs as soon as the device contacts with water.

References

[1] M. Speers, C. Bonnano, Economic aspects of controlled drug delivery. Encyclopedia of Controlled Drug Delivery New York, NY: Wiley. (1999) 341-347.

[2] R. Verma, B. Mishra, S. Garg, Drug Dev. Ind. Pharm. 26 (2000) 695-708.

[3] R.K. Verma, D.M. Krishna, S. Garg J. Controlled Release. 79 (2002) 7-27.

[4] J. Shokri, M.H. Zarrintan, S. Ghanbarzadeh, Z. Arash, A. Farahani, K. Adibkia, Drug Res. 63 (2013) 414-419.

[5] F. Theeuwes J. Pharm. Sci. 64 (1975) 1987-1991.

[6] W. Gong, Y. Liu, D-Y. Mei, M. Yang, X-G. Mei. Drug Dev. Ind. Pharm. 41 (2015) 464-469.

[7] M. Mathu, R. Mishra, Int J Pharm Sci Res. 7 (2016) 453.

[8] L. Liu, J. Ku, G. Khang, B. Lee, J.M. Rhee, H.B. Lee, J. Controlled Release. 68 (2000) 145-156.

[9] Z-H. Zhang, H-Y Dong, B. Peng, H-F Liu, C-L Li, M. Liang, Int. J. Pharm. 410 (2011) 41-47.

[10] V. Malaterre, J. Ogorka, N. Loggia, R. Gurny, Int. J. Pharm. 376 (2009) 56-62.

[11] J. Shokri, J. Hanaei, K. Adibkia, M.H. Zarrintan, M. Mehrpouya Pharm Sci. 1 (2004) 75-86.

[12] Y. Yang, Z. Zhao, Y. Wang, L. Yang, D. Liu, X. Yang, Int. J. Pharm. 506 (2016) 340-350.

[13] H.P. Thakkar, N. Pancholi, C.V. Patel, AAPS Pharm Sci Tech. 17 (2015)1-13.

[14] C.K. Sahoo, N.K.Sahoo, S.R.M. Rao, M. Sudhakar, K. Satyanarayana, Bulletin of Faculty of Pharmacy, Cairo University. 53 (2015) 195-205.

[15] A.A. McKinney, G.D. Tollefson, E. Weber, R. Soltero, US Patents 20130177602 A1, 2012 .

[16] N. Jain, R. Sareen, N. Mahindroo, K. Dhar, The Scientific World Journal. (2014) Article ID 438528.

[17] A. Thombre, L. Appel, M. Chidlaw, P. Daugherity, F. Dumont, L. Evans, J. Controlled Release. 94 (2004) 75-89.

[18] J. Shokri, P. Ahmadi, P. Rashidi, M. Shahsavari, A. Rajabi-Siahboomi, A. Nokhodchi, Eur. J. Pharm. and Biopharm. 68 (2008) 289-297.

[19] A. Nokhodchi, M.N. Momin, J. Shokri, M. Shahsavari, P. Rashidi, Drug Delivery. 15 (2008) 43-48.

[20] F. Theeuwes, R.J. Saunders, W.S. Mefford Process for forming outlet passageways in pills using a laser. US patent 4088864 A, 1978.

[21] S.N. Makhija, P.R. Vavia, J Controlled Release. 89 (2003) 5-18.

[22] P. Kanagale, B.B. Lohray, A. Misra, P. Davadra, R. Kini, AAPS Pharm Sci Tech. 8 (2007) E13-E9.

[23] A. Abd-Elbary, M.I. Tadros, A.A. Alaa-Eldin, AAPS Pharm Sci Tech. 12 (2011) 485-495.

[24] R.A. Keraliya, C. Patel, P. Patel, V. Keraliya, T.G. Soni, R.C. Pate, lISRN Pharmaceutics. (2012) Article ID 528079: 1-9.

[25] J. Shokri, K. Adibkia, Cellulose-Medical, Pharmaceutical and Electronic Applications, Theo EDs. van de Ven and Louis Godbout. InTech, 2012.

[26] K. Adibkia, J. Hanaee, S. Ghanbarzadeh, R. Bahrami, J. Shokri, Drug Res. 64 (2014) 203-237.

[27] G.M. Zentner, G.S. Rork, K.J. Himmelstein J. Controlled Release. 1 (1985) 269-282.

[28] A.G. Thombre, G.M. Zentner, K.J. HimmelsteinJ. Membrane Sci.40 (1989) 279-310.

[29] S. Sharma, P. Sher, S. Badve, A.P. Pawar. AAPS PharmSciTech, 6, Issue 4 (2005) 618-625.

[30] J. Hirvonen, T. Laaksonen, L. Peltonen, H. Santos, V.P. Lehto, T. Heikkilä, J. Riikonen, J.

Salonen. Dosis, 24 (2008) 129- 149.

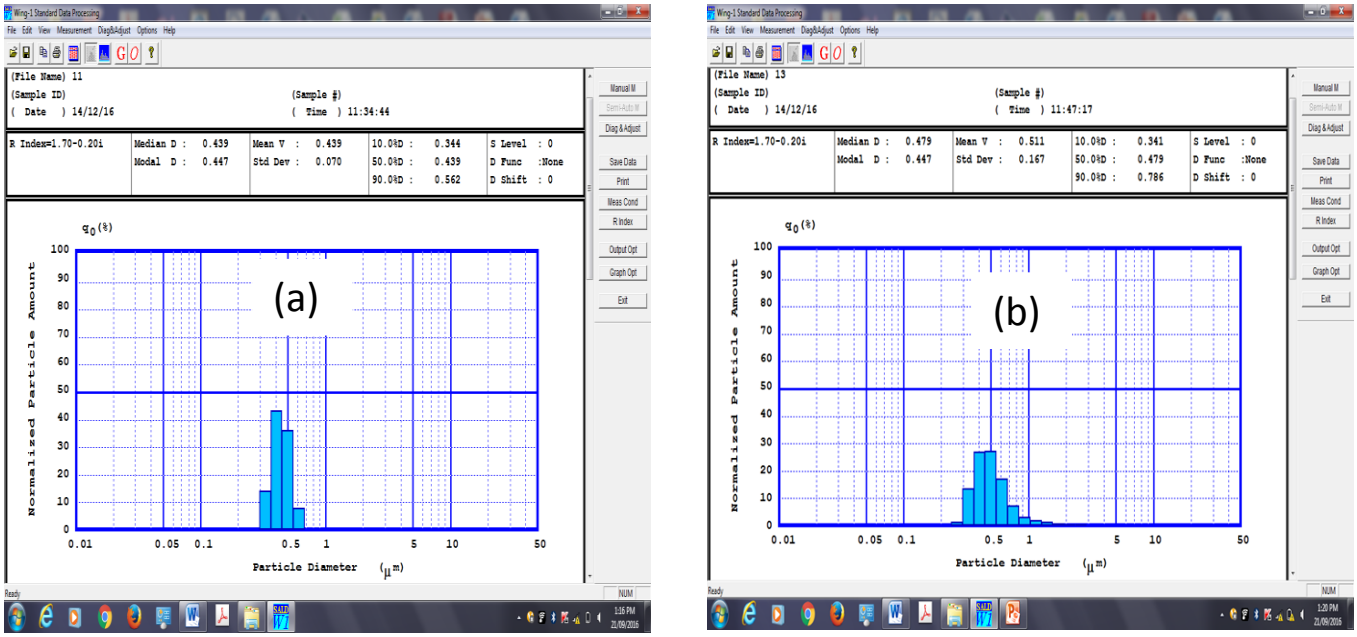


Figure 1. Size of sucrose (a) and mannitol (b) suspended in acetone/ethanol mixture after grinding in ball-mill.

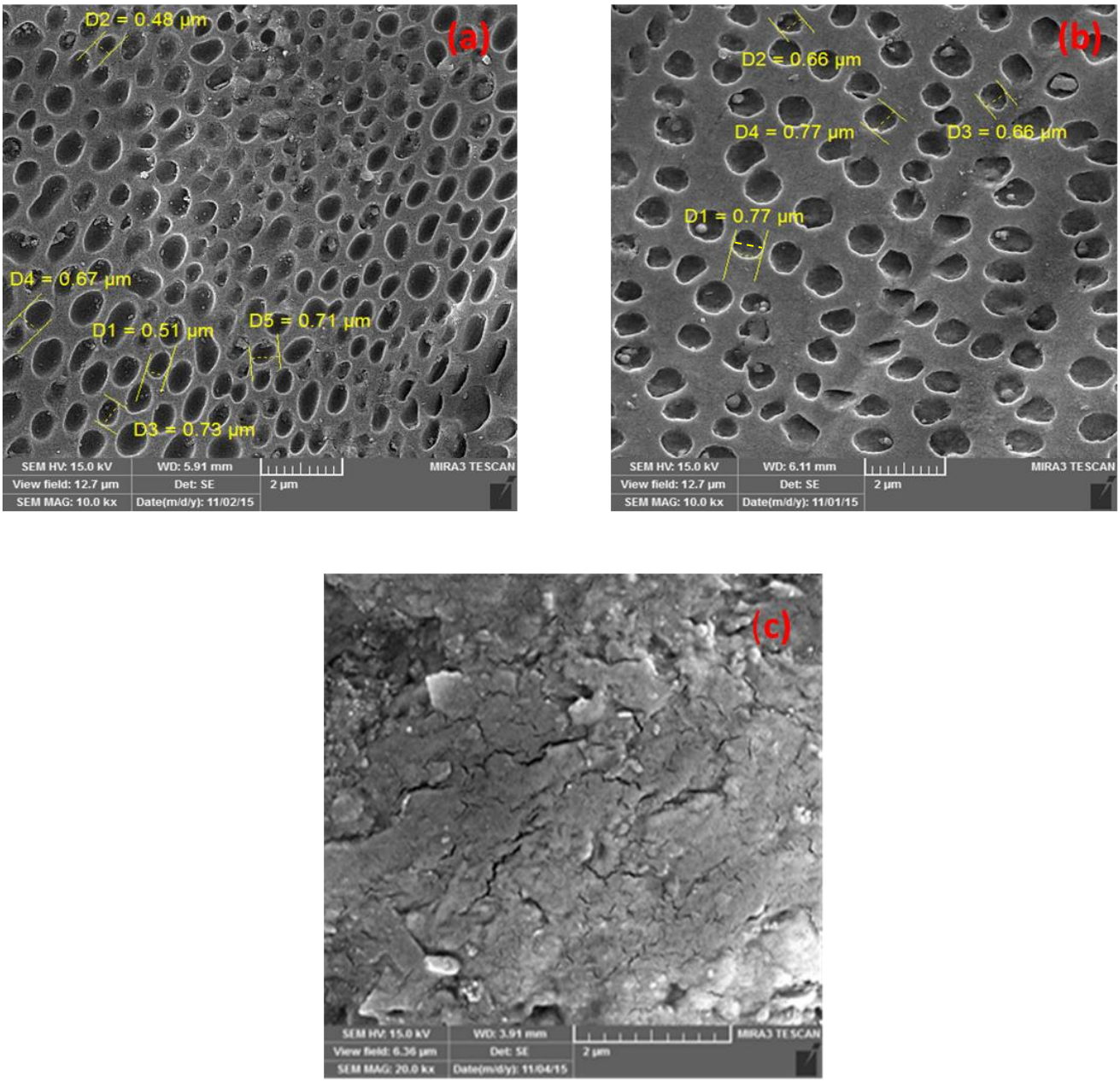


Figure 2. SEM images of (a) mannitol, (b) sucrose containing SPM and (c) blank (SPM without pore formers) after dissolution run.

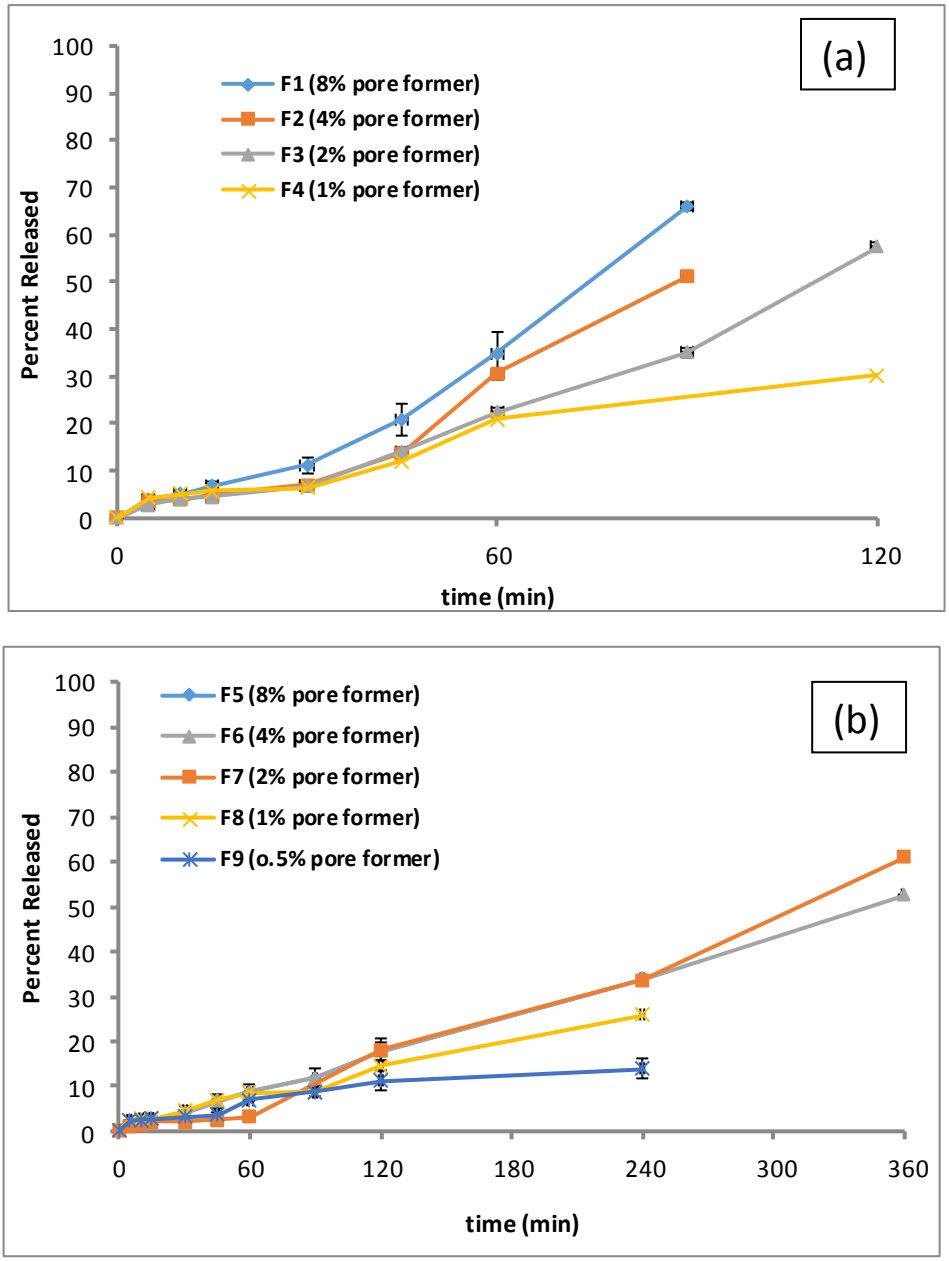
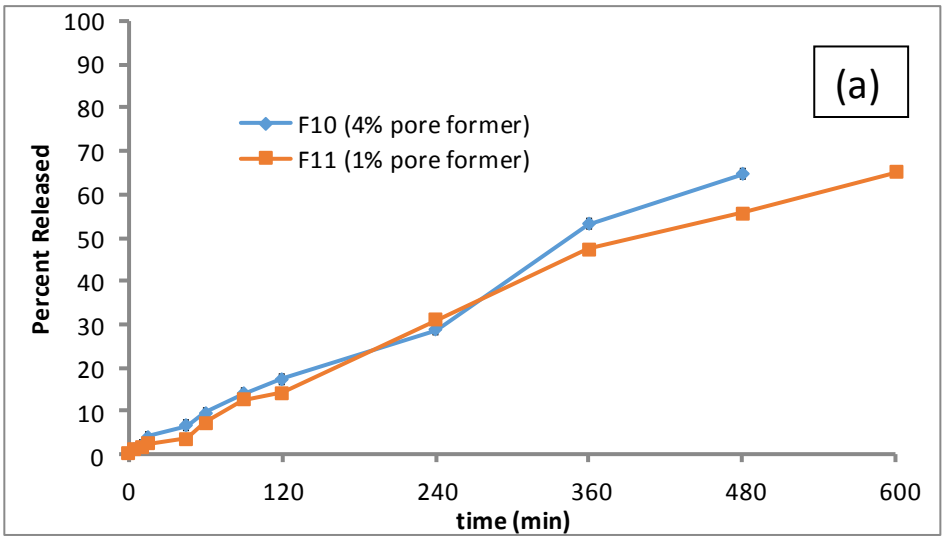


Figure 3. Release profiles of (a) F1-F4 containing different amounts of pore former in SPM, 175 mg osmotic agent and 50 mg HPMC; (b) F5-F9 containing different amounts of pore former in SPM, 100 mg osmotic agent and 50 mg HPMC in core formulation(n=3; error bars are standard deviation).



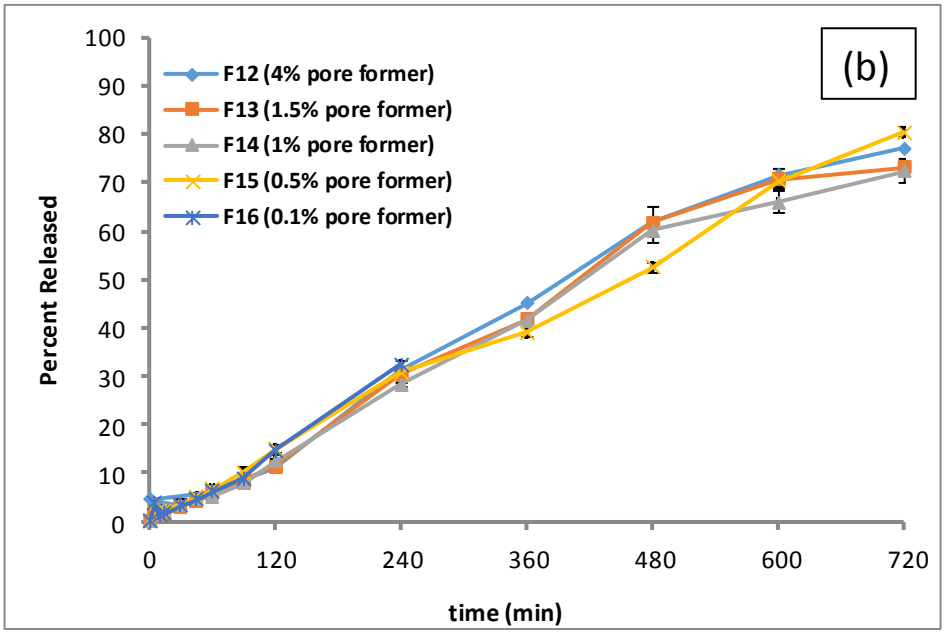


Figure 4. Release profiles of (a) F10-F11 containing different amounts of pore former in SPM and 20mg HPMC in core formulation; (b) F12-F16 containing different amounts of pore former in SPM and 10 mg HPMC in core formulation (n=3; error bars are standard deviation).

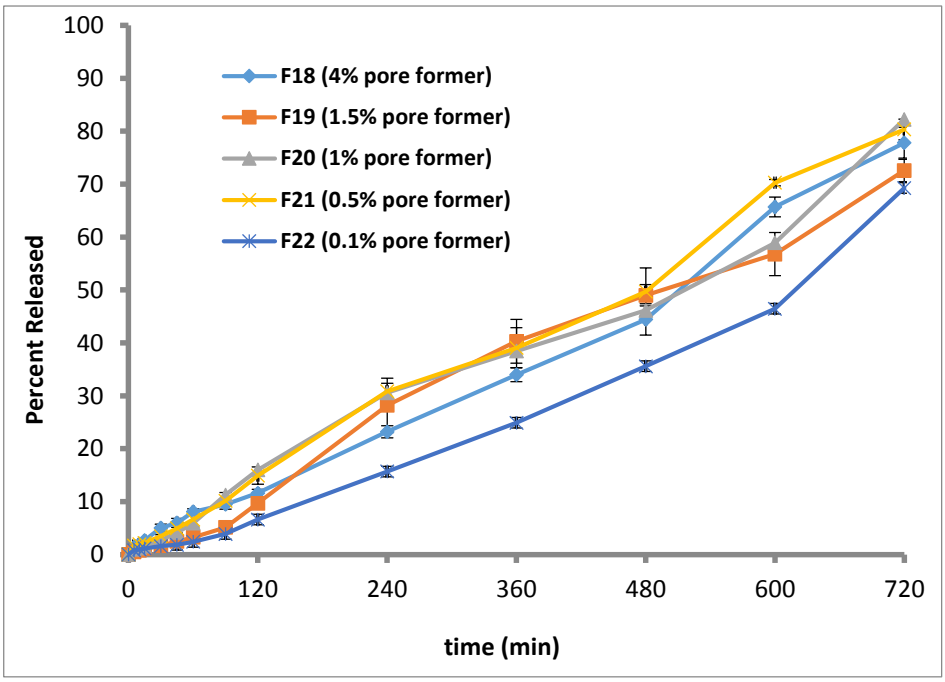


Figure 5. Release profiles of F18-F22 containing different amounts of pore former in SPM and without HPMC in core formulation ((n=3; error bars are standard deviation).

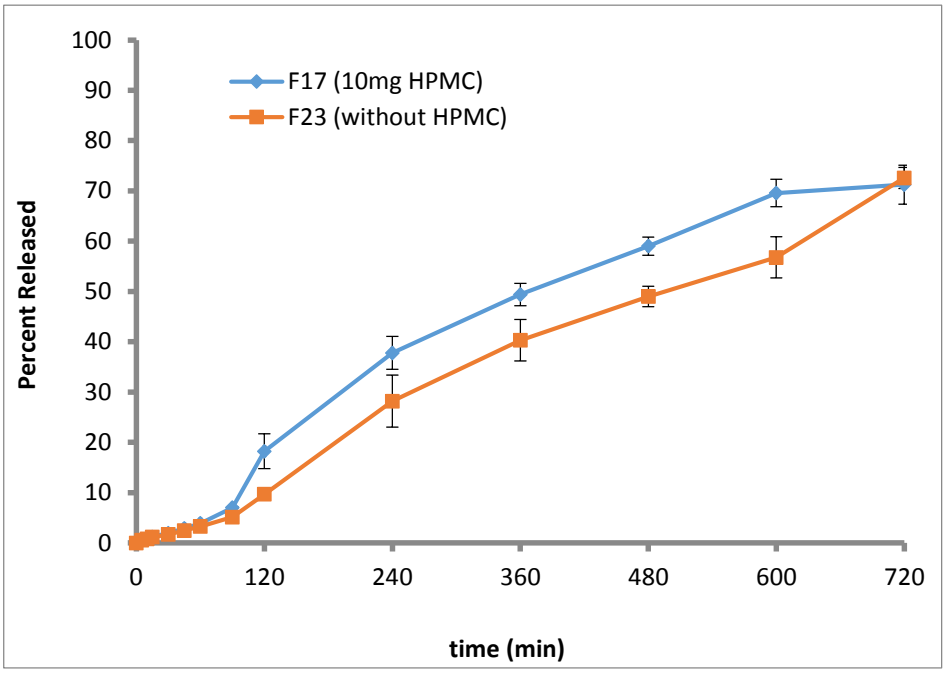


Figure 6. Release profiles of F17 and F23 with different amounts of HPMC in core formulation (n=3; error bars are standard deviation).

Table 1. Core and SPM composition of different formulations (all formulations contained 20 mg 4-Amino pyridine in core and 6% w/v cellulose acetate 3% w/v castor oil and 2% w/v PEG200 in SPM).

Formulation Code	Core Composition					SPM Composition	
	HPMC	Lactose	Sucrose	Avicel	Talc	Sucrose (%)	Mannitol (%)
F1	50	150	175	90	-	8	-
F2	50	150	175	90	-	4	-
F3	50	150	175	90	-	2	-
F4	50	150	100	90	-	1	-
F5	50	150	100	90	75	8	-
F6	50	150	100	90	75	4	-
F7	50	150	100	90	75	2	-
F8	50	150	100	90	75	1	-
F9	50	150	100	90	75	0.5	-
F10	20	150	100	90	105	4	
F11	20	150	100	90	105	1	-
F12	10	150	100	90	115	4	
F13	10	150	100	90	115	1.5	-
F14	10	150	100	90	115	1	-
F15	10	150	100	90	115	0.5	-
F16	10	150	100	90	115	0.1	-
F17	10	150	100	90	115	-	0.5
F18	0	150	100	90	125	4	-
F19	0	150	100	90	125	1.5	-
F20	0	150	100	90		1	-
F21	0	150	100	90	125	0.5	-
F22	0	150	100	90	125	0.1	-
F23	0	150	100	90	125	-	0.5
F24	0	150	100	90	125	-	-

Table 2. Release parameters for the selected formulations.

Formulation Code	RSQ_{zero}	$D_{12\ h}$ (%)	t_L (h)	Dev_{zero} (%)	Release Rate (mg/h)
F13	0.98	73.19	-0.02	0.15	6.10
F14	0.99	72.29	-0.06	14.70	6.02
F15	0.99	80.37	-0.08	9.24	6.70
F19	0.99	72.58	-0.16	37.89	6.05
F20	0.98	82.23	-0.07	14.5	6.85
F21	0.99	80.33	-0.08	0.13	6.69
F22	0.97	69.26	0.39	0.75	5.77
F23	0.99	72.58	0.14	0.21	6.05
F17	0.97	71.26	-0.11	49.93	5.94